ability to fend off HPV infection, but the available data do suggest that HPV vaccines would provide a lengthy period of protection, likely to usher a vaccinated individual through the years of highest infection risk and beyond. Additional studies are ongoing to verify these projections. Based on demonstrated clinical efficacy and favorable safety profile, this quadrivalent HPV prophylactic vaccine is being introduced as a cost-effective means for reducing the morbidity and mortality of cervical/anogenital cancers, as well as the emotional and economic burdens of abnormal Pap tests and genital warts. Compared to a vaccine containing VLPs of only HPV types 16 and 18, the reduction of HPV-associated disease burden is anticipated to be significantly higher with the administration of the quadrivalent HPV vaccine, since HPV 6 and 11 are responsible for approximately 90% of all genital warts and 15% of low-grade cervical neoplasias. The quadrivalent HPV vaccine is the first and only to show 100% efficacy against HPV 6, 11, 16 and 18-related external genital lesions including genital warts, vulvar and vaginal cancers. Moreover, the prevention and cost-savings from HPV 6/11 related diseases will begin relatively early in the first years following vaccine introduction making the quadrivalent vaccine particularly attractive to national policy-makers.

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Intradermal Route: The Natural Pathway for Improved Influenza Vaccination (invited)

29.001

Global Use of Seasonal Influenza Vaccine

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For several years, the Macroepidemiology of Influenza Vaccination Study Group (MIVSG) has documented influenza vaccine distribution, recommendations and reimbursement in an increasing number of countries throughout the world. In 2003, 56 MIVSG countries used 275 million (M) doses, 94% of the 292 M doses distributed worldwide. By 2005, the MIVSG had grown to include 73 countries. These countries used approximately 330 M doses of seasonal vaccine. In most countries, levels of vaccine use (doses distributed/1000 total population) showed relatively little change between 2002, the year before the re-emergence of H5N1 influenza, and 2005, although large differences persisted between individual countries. However, six countries (Belgium, El Salvador, Japan, Latvia, Malta and Mexico) showed substantial increases in vaccine use over this period, and Malta's increase from 124 to 657 doses/1000 was remarkable. In a few countries, vaccine use decreased, sometimes due to supply shortages. Some form of public reimbursement for vaccination was provided in approximately 60% of the surveyed countries, and they tended to have higher levels of vaccine use compared with countries with no public reimbursement. Vaccination recommendations for risk groups showed little change compared with earlier years, although the age cut-off levels for vaccinating older adults decreased in several countries. More interesting, by 2005, seven countries was extended to 5 years in 2006 and to 18 years in 2008.

In 2005, nine vaccine-producing countries used 59% of all doses of seasonal influenza vaccine, but had only 12% of the world's population. Influenza vaccination is gradually increasing in many countries, especially in those with rapidly developing economies. This growth in seasonal vaccine use will lay the foundation for vaccination programs when the next pandemic occurs.

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29.002

The Potential Benefits of Intradermal Vaccination

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The intradermal (ID) route of immunization has a fair claim to primacy since the smallpox vaccine was administered via the skin for almost 100 years before the next human vaccine was introduced. Despite this early success and long-standing immunological interest in this route, the large majority of current vaccines are administered either via the intramuscular or subcutaneous routes. The accessibility of the skin is obvious and the potential immunological advantages of ID immunization have been known for some time. Animal models of ID vaccination have generally yielded excellent results with a range of microbial antigens and several ID vaccines have been successfully introduced for human infections such as rabies and hepatitis B. The skin is the largest immune 'organ' of the human body and, unlike subcutaneous and muscle tissues, the skin has evolved specifically to limit the penetration of chemical and microorganisms. As a result, the skin is better prepared than most tissues to actively screen for invasive microbes and to mount appropriate innate and adaptive immune responses. The immunologic characteristics and capabilities of the skin have been the subject of considerable research for many years due to this unique 'front line' position. Until recently however, full exploitation of the potential of the ID route for vaccination has been hampered by the lack of simple, reliable and safe injection systems. Recent advances in delivery system technologies have sparked renewed interest in the ID route for both established and new vaccines. This presentation will provide an overview of the potential immunological and practical advantages of ID vaccination as well as a brief review of historical and recent ID vaccination techniques.

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29.003

Clinical Development of a Seasonal Influenza Vaccine by Intradermal Micro-injection

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Background: Annual trivalent inactivated influenza vaccines (TIV) provide protection for hundreds of millions of individuals worldwide. Yet there is need to improve vaccine efficacy

for the elderly who are most affected by influenza, and to increase vaccine coverage in younger adults. The intradermal route of vaccination provides a direct and potentially more efficient access to the immune system. An ID TIV was developed with a unique, convenient microinjection system, and 2 dosage presentations specifically for elderly and younger adults (respectively 15 μg or 9 μg hemagglutinin/strain/dose).

Methods: The immunogenicity and safety of the two presentations of ID TIV have been investigated in several large-scale Phase 2 and 3 studies in several European countries, Australia and New Zealand. In each study, a licensed intramuscular TIV, (Vaxigrip®; 15 μg hemagglutinin/strain/dose) was used as a control. Safety evaluation included documentation of solicited and unsolicited reactions. Hemagglutination inhibition responses were evaluated on D0 and D21.

Results: Phase 2 studies in more than 2000 subjects aged 18—60 years or >60 years have demonstrated that the 15 μg ID intradermal vaccination induces higher immune responses compared with Vaxigrip against all three strains, as assessed by D21 GMTs and seroprotection rates. Among younger adults, the 9 μg intradermal vaccine was demonstrated to induce an equivalent immune response to Vaxigrip.

Safety results showed that both ID vaccine presentations were well tolerated. When 18—60 year olds, subjects were vaccinated a second time either ID or IM, one year after their first vaccination, reactogenicity was not enhanced compared with that observed after the first vaccination.

Conclusion: Using microinjection to deliver antigen via the less-invasive intradermal route, ID TIV was shown to elicit superior immune responses to conventional vaccine in elderly adults, and provides an alternative vaccine for adults that may encourage increased vaccine uptake.

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29.004

From Immunogenicity to Vaccine Efficacy: Insights from Statistical and Causal Models

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Background & Objectives: The identification of immunological surrogate markers of protection against disease plays a key role in the assessment of the efficacy of any vaccine. The sole identification of an appropriate surrogate marker is however not sufficient to provide an accurate prediction of vaccine efficacy. A statistical model providing a reliable estimation of the relationship between this marker and clinical protection is also required. We review analyses and models that explore this relationship in the case of influenza. We then discuss the application of such models to estimate the gain in efficacy provided by a novel seasonal influenza vaccine given by intradermal microinjection.

Methods & Principal findings: Several markers have been used to assess the immunogenicity of influenza vaccines. Anti-haemagglutinin antibodies, measured by the haemagglutination inhibition (HI) assay is however the only one for which attempts have been made to quantify its relationship with protection against clinical influenza. Seminal analyses focused on the identification of an HI titre level that can be associated with either a 50% reduction (1:40) or a 90% reduction (1:92) in the risk of influenza. More recently, a model using published data from 15 studies, confirmed the significant and positive relationship existing between HI titre and clinical protection against influenza and provided an estimate of the level of protection against influenza for any HI titer. When applied to immunogenicity data from clinical trials with an trivalent, inactivate influenza vaccine given by intradermal microinjection, this model predicts a gain in vaccine efficacy of 14% (95% CI: 10—18) compared with conventional non-adjuvanted inactivated influenza vaccines given intramuscularly.

Conclusions: Statistical models estimating the relationship between HI data and level of protection against influenza provide useful information to predict vaccine efficacy, particularly for comparing vaccines based on their immunological profile.

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Viral Hepatitis (invited)

30.001

Treatment of Hepatitis C: Yesterday, Today, and Tomorrow

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Approximately 170 million people world wide are infected with Hepatitis C virus (HCV). The therapy of hepatitis C has gone through various phases of development. In the early 90s, therapy was empirical and standard interferon was given initially for 6 months and then for 12 months. Then came along ribavirin, a guanosine analog and an oral drug, which administered with interferon improved sustained virologic response rates and this primarily was achieved by decreasing relapse rates. The current standard of care as therapy for Hepatitis C consists of pegylated interferon-alfa and ribavirin. In genotype 1 patients, sustained virologic response rates have been around 40—60% after 48 weeks of therapy whereas non-1 patients, primarily made up of genotypes 2 and 3, have an approximate 80% probability of sustained virology response after 24 weeks of therapy. Although treatment duration has traditionally been fixed, there is a paradigm of virologic response guided therapy that has evolved. For rapid virologic responders, characterized as HCV RNA negativity at week 4, reports suggest that 12—16 weeks of therapy for genotype 2 patients and 24 weeks of therapy for genotype 1 patients may be adequate. In contrast, in genotype 1 patients who have a slow response characterized by a loss of HCV RNA at week 24, a prolonged course of 72 weeks is the optimal regimen. Despite these advances, there is an unmet need for better therapies in the non-responders, in those with advanced and decompensated liver disease, in those with a spectrum of special situations such as transplantation etc, and those who do not tolerate interferon and ribavirin. Thus there is a need for novel therapies with enhanced efficacy, tolerability, and greater ease of administration.

We now stand at the edge of an exciting phase with the advent of Specifically Targeted Antiviral Therapy for